REMARKS

Claims 20-23, 26 and 28-29 have been canceled to simplify prosecution. As the amendment proposed only cancellation of claims, entry of the amendment at this stage of prosecution is believed proper.

Applicants respond to the outstanding grounds for rejection as follows:

Claims 20-23, 25-29 (sic, 26 and 28-29), 37 and 38 (sic, 38 is canceled) were rejected as assertedly anticipated by Contag (US 5,650,153). This basis for rejection is moot except as it is applied to claim 37. The Office asserts that the features of claim 37 are disclosed in Contag by assembling the disclosure set forth in column 9, lines 29-40, with the disclosure in column 12, lines 19-31, and column 14, lines 58-65. However, applicants believe that the assembly of these elements in the manner suggested by the Office is not sufficient to provide anticipation of the invention as claimed by Contag.

It is black-letter law that each and every limitation of the claim must be found explicitly or inherently in a single prior art document in order for anticipation to be found. In order to anticipate, this disclosure must not only disclose the individual elements of the invention, but must connect them in the manner required by the claim. The recent case of *Hyatt v. Dudas*, 83 USPQ2d 1373 (Fed. Cir. 2007) illustrates this. In that case, the applicant claimed a combination of elements. The applicant identified disclosures of all of the separate elements in his application, putatively in support of a claim that was directed to these elements connected with each other. The Office required the applicant to demonstrate where in the application such a connection was described. The Federal Circuit upheld the position of the Office, that it was insufficient disclosure of a claimed

combination to disclose the elements of the combination separately and not indicate the manner in which they are connected. That appears to be the case with regard to Contag.

First, the portion of Contag in column 12, beginning at line 19, does not describe any method to screen for a modulator of the expression of a gene in a multicellular organism by comparing expression of a fluorophore under the direction of the promoter of an endogenous gene in the presence and absence of a modulator. Rather, to the extent that paragraph in Contag can be understood, it is directed to something else entirely. Apparently, a gene encoding a light-generating molecule (not necessarily fluorophore) under the control of a selected promoter which is effective in cells to be targeted by a therapeutic gene is monitored. Presumably this is on the same vector as a therapeutic gene and the assumption is made that production of the light-generating molecule somehow is able to determine not only the location of the therapeutic gene (which makes sense, since it is on the same vector) but also the level of expression of the therapeutic gene. Since, apparently, the therapeutic gene is not under control of the same promoter, it is unclear how this would be done. In any case, it does not describe the method of the invention even if the light-generating molecule is considered a fluorescent protein.

The paragraph in column 14, beginning at line 58, is more related in that an endogenous promoter is indeed used to drive the production of luciferase. However, as argued extensively in the previous response, the expression of luciferase as an indicator is specifically excluded from the present claims because the fluorophore must be a protein that is autofluorescent such that no substrates or cofactors are needed for it to fluoresce.

However, the Office takes the position that the disclosure in column 14 is not limited to luciferase because column 9, beginning at line 29, refers to additional fluorescent moieties, only

some of which are fluorescent proteins. It is unclear from the paragraph in column 9 how these alternative fluorescent molecules are to be used. Some of them, such as fluorescein, are clearly unable to be generated by the action of a promoter. Therefore, as was the case in *Hyatt v. Dudas*, there is no specific connection between the general discussion in column 9 of fluorescent moieties and the discussion in column 14, which is specific to luciferase.

As a result, there is no explicit discussion of testing modulating substances by virtue of their effect on a construct which contains an endogenous promoter coupled to a fluorescent protein. The description, if any, is merely inherent.

As set forth in MPEP § 2112(IV), the fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish inherency. As quoted from *In re Oelrich*, 666 F2d 578, 212 USPQ 323, (CCPA 1981), inherency may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.

In the present case, clearly the coupling of an endogenous promoter to a fluorescent protein in Contag is not an inevitable result. Rather, the coupling of a luciferase to an endogenous promoter is the only inevitable result described in Contag. For this reason, the rejection of claim 37 over Contag may be withdrawn.

Claims 20-23, 26 and 28 (applicants assume the Office intends to include claim 29) were rejected as assertedly failing to comply with the written description requirement. This basis for rejection is moot in view of the cancellation of these claims.

Claims 39 and 40 were rejected as assertedly lacking enablement in the specification. In reviewing the basis for rejection as set forth in the previous Office action, it appears that the *Wand*

factors cited are assembled, not to show that one skilled in the art would not know how to administer a mutation-inducing agent to a non-human multicellular organism or would not know how to construct a multicellular organism that expresses a fluorophore under the direction of a promoter of an endogenous gene or to determine the expression of the promoter by, following the teachings of the invention, observing the presence, absence or intensity of the fluorescence generated by the fluorophore at various locations by whole-body external fluorescent optical imaging or carrying out the foregoing steps in a multicellular animal that has not been administered a mutation-inducing agent for comparison, or would not know how to compare the expression levels in the treated and untreated organisms based on fluorescence.

Other than mere breadth, which is not a valid basis (taken alone) for rejection, the substantive basis for this appears to be the complexity of the animal system whereby the results obtained might not lead unambiguously to the conclusion desired by the preamble. No doubt transgenic animals are complex systems and there are many interactions involved. However, the Office has offered no evidence that a change in expression, as evidenced by the level of fluorescence in a treated *versus* an untreated animal, would not (as asserted by applicants) indicate that the gene was altered or that the absence of a difference in level of expression would indicate that it is not. Even if the mutation agent influenced other gene products, the likelihood that these products would so distort the result that even a qualitative answer could not be obtained seems highly unlikely. Absent some evidence of record that the method of the invention would not work as described, applicants believe the Office is obliged to acknowledge the truth of the disclosure set forth in the specification (*In re Marzocchi*, 439 F2d 220, 169 USPQ 367 (CCPA 1971).

These arguments have been acknowledged in the present Office action and applicants appreciate the agreement that there is no requirement for a working example in order for the description of the invention to be enabling.

Applicants appreciate that the Office does not expect the screening method to be foolproof and has acknowledged that methods of making transgenic animals are known in the art.

However, the Office notes that a transgenic animal that has a certain phenotype is merely a result of "trial and error." Respectfully, applicants believe this is not the case in the present situation. The only "phenotype" that needs to be obtained is the expression of the fluorescent protein coupled to the endogenous promoter. This has been illustrated over and over again, not only in the present application but in the prior art. So, all that is left is the argument that the results will be so undermined by the possible interactions with other gene products that the test is useless. Again, the Office has produced no evidence that this is the case.

Enclosed herewith is the Declaration of Dr. Robert Hoffman (executed copy to follow tomorrow) which provides the evaluation of an expert in this art as to whether meaningful results can be obtained using the claimed method. As noted, there is no history of other gene products interfering with a fluorescent protein generated in situ and controls are readily available to assure that it is not. Again, applicants emphasize that there appears to be no dispute that the artisan would be able to carry out the required steps and the only issue is whether the results can be interpreted satisfactorily.

In view of the foregoing, it is believed that this basis for rejection may also be withdrawn.

Conclusion

Only claims 37 and 39-40 remain in the case. The sole basis for rejection of claim 37 is asserted anticipation by Contag which, as demonstrated above, is in error because while Contag separately discloses features of the invention, Contag fails to connect them in the manner required by the claim. Claims 39-40 are rejected only on the basis of lack of enablement which is essentially a rejection based on lack of utility. There is no dispute that the claim steps can be carried out successfully, only that the results may not be correctly interpreted. As noted above, the Office has supplied no evidence that the transgenic animal system is so incapable of yielding meaningful results that no conclusion can be drawn from the results of carrying out the method. Instead, the Office has merely conjectured a possibility of one element that might interfere quantitatively, but not necessarily qualitatively with the interpretation of the results.

Thus, applicants believe claims 37 and 39-40 are in a position for allowance and passage of these claims to issue is respectfully requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 312762002710.

Respectfully submitted,

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